



## Butler Journal of Undergraduate Research

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Volume 2

Article 21

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2016

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### Recommended Citation

Coffinger, Sean P. (2016) "Moderate Ethanol Consumption Results in Cognitive Protection from Alzheimer's Disease, Dementia, and Related Cognitive Decline: A Critical Review," *Butler Journal of Undergraduate Research*: Vol. 2, Article 21.  
Available at: <http://digitalcommons.butler.edu/bjur/vol2/iss1/21>

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# **MODERATE ETHANOL CONSUMPTION RESULTS IN COGNITIVE PROTECTION FROM ALZHEIMER'S DISEASE, DEMENTIA, AND RELATED COGNITIVE DECLINE: A CRITICAL REVIEW**

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MENTOR: ADAM BRICKMAN

## **Abstract**

Moderate ethanol preconditioning, a result of prolonged moderate alcohol intake, serves as a protective process by staving off cognitive decline while providing neuronal protection through several mechanisms. These individual mechanisms are relatively well known, however a comprehensive and integrated conversation of ethanol's protective tendencies is lacking from literature and the field of neuroscience. First, a review of the leading theories behind moderate ethanol preconditioning's biological and cognitive benefits is presented, including overviews of neuroprotective, antioxidant, and neurotropic mechanisms responsible for neurological benefit. Secondly, an integrative model is presented, incorporating all research into a novel collaborative model. An additional discussion regarding the efficacy of ethanol treatments follow the comprehensive and integrated model.

## **Introduction**

Current Alzheimer's disease (AD) projections estimate prevalence rates to quadruple by 2047, inevitably resulting in the diagnosis of nearly 1 in 45 Americans over the next three decades (Herbert *et al.*, 2003). AD is the sixth leading cause of death in the United States, and will soon establish itself as an even greater social and economic burden. In attempt to mitigate this impending affliction, extensive research has been conducted in identifying potential risk factors and protectants for the AD pathology and associated cognitive decline. Some prominent risk factors have been identified as obesity (Whitmer *et al.*, 2008), elevated cholesterol levels (Soloman *et al.*, 2009), vascular conditions such as diabetes and hypertension (Richard *et al.*, 2012), family history of the pathology (Lautenschlager *et al.*, 1996), and traumatic brain injury (Giunta *et al.*, 2012). Additionally, cardiovascular exercise (Agevaren *et al.*, 2008) and healthy diet containing proper nutrients (Gu *et*

*al.*, 2010) can serve as effect promoters of cognitive functioning and protect individuals from cognitive decline and dementia. One possible protective factor, in particular interest to this paper, has raised much debate within the aging and mental health research community: Alcohol consumption.

Numerous studies have shown a protective effect of alcohol intake on cognitive decline and AD related dementia (Peters *et al.*, 2008; Piazza-Garner *et al.*, 2013; Anstey *et al.*, 2009). In this critical review, we will examine alcohol's effects on AD and cognitive function starting from the cellular level before expanding our search for broader implications. Additionally, this paper will be focusing exclusively on ethanol's effects in aging and cognitive decline. All consumable alcohol contains ethanol, which must be investigated independently in order to control for the wide variety of beverages consumed (e.g. wine or beer). For example, wine inherently contains components such as polyphenols that could enhance its protective effects (Wang *et al.*, 2006). Polyphenols and other proposed beneficial components of alcoholic beverages will not be discussed further, and the interaction between ethanol and the AD pathology will be exclusively investigated. Furthermore, some proponents suggest that ethanol is the sole contributor to alcohol's protective effects, even in wines (Klatsky *et al.*, 1997). This established, this paper has three main goals: (1) investigate ethanol's protective effects at the cellular level and suggest a new integrated biological model scheme, (2) identify additional methods in which ethanol could serve as a protectant, and (3) determine if ethanol could be used as an appropriate intervention for cognitive decline associated with AD related dementia.

### **Moderate Ethanol Preconditioning**

The biological response to ethanol consumption must be examined in order to understand the cognitive benefits of alcohol ingestion. Therefore, we must first investigate ethanol's neurobiological impact. It is known that subjecting a biological construct to repeated subtoxic injury over time can result in a phenomenon known as *Preconditioning* (Kalev-Zylinska *et al.*, 2007). Preconditioning is the leading theory of how ethanol helps preserve our cognitive functioning and serves as an active neuroprotective agent. Ethanol conditions a particular glutamate receptor, the N-methyl-D-aspartate receptor (NMDAR), by acting as an antagonist. When individuals consume alcohol at a moderate/low-level over a long period of time, NMDAR is conditioned to this constant suppression, ultimately resulting in upregulation and increased activation of the receptor (Kalev-Zylinska *et al.*, 2007). This

paradoxical process is called *Moderate Ethanol Preconditioning* (MEP). Once the NMDAR establishes a chronic increase in activation, a direct result of MEP, several downstream processes begin that result in the production of multiple protective factors that combat AD pathology, dementia, and cognitive decline. This established, we will now review the specific mechanisms downstream from MEP and determine the particular biological consequences of chronic low-level ethanol intake.

### **MEP: NEUROPROTECTIVE MECHANISM**

Moderate ethanol consumption may combat emerging cognitive decline during aging and AD by targeting neuroinflammation related to amyloidogenic protein accumulation. This accumulation of  $\beta$ -amyloid ( $A\beta$ ) is responsible for the plaques seen in AD, neurodegeneration caused by increases in  $Ca^{2+}$ , and proinflammatory mediators (Collins *et al.*, 2010). In order to effectively combat  $A\beta$  toxicity through MEP, NMDAR activity must create a downstream byproduct that directly affects neurodegeneration caused by this protein aggregation. In Vitro studies targeting hippocampal-entorhinal cortical (HEC) slices have discovered one method of neuroprotection via increases in NMDAR activity, resulting in the production of heat shock protein 70 (HSP70) (Collins *et al.*, 2010). HSP70 levels highly correlate with protection against various cell-damaging outcomes, including ischemia, glutamate excitotoxicity, and reactive oxygen species (Belmandani *et al.*, 2004). Furthermore, it is suggested that HSP70 directly inhibits apoptosis by diminishing  $A\beta$ 's neurotoxicity (Belmandani *et al.*, 2004). Although they are correlated, the downstream process from NMDAR activity to upregulation of HSP70 is not direct, and requires the involvement of mediators. These mediating factors must be established in order to sufficiently understand ethanol's part in HSP70 production.

After successfully preconditioning HEC slices (subjecting cultures to 20-30 mM ethanol for 6 days), immunoblot analyses showed significant upregulation of all NDMAR subunits (NR1, NR2B, NR2C) (Collins *et al.*, 2010). After inducing MEP, several possible mediators were measured at days 2, 4, and 6. One protein in particular, Protein Kinase C epsilon type (PKC $\epsilon$ ), highly correlated with the up regulation of the NMDAR and showed increases of 15% (at day 2), 40% (at day 4), and 200% (at day 6) (Collins *et al.*, 2010). This large increase suggests that PKC $\epsilon$  is directly downstream from NMDAR and is further established by a NR1 knockdown using memantine, which simultaneously antagonized both the NMDAR and PKC $\epsilon$  expressions. Additionally, the use of a pan-PKC inhibitor significantly suppressed both

PKC $\epsilon$  and HSP70, further restoring toxicity and establishing PKC $\epsilon$  as an upstream mediator of HSP70 (Collins *et al.*, 2010). However, the link between PKC $\epsilon$  and HSP70 still requires upregulation of one more mediator, focal adhesion kinase (FAK). Western blot analyses of FAK in HEC cultures showed a significantly increase that correlated flawlessly with PKC $\epsilon$  upregulation (Collins *et al.*, 2010). Additionally, using PKC isoforms, Collins *et al.*, (2010) were able to show that PKC $\epsilon$  was at least indirectly responsible for the increases in FAK (Collins *et al.*, 2010). Furthermore, the use of the dominant negative FAK (FRNK) was used to establish the link between FAK and HSP70. FRNK expression greatly reduced MEP-mediated increases in HSP70 (Collins *et al.*, 2010). These findings result in the neuroprotective upregulation of HSP70 that began with the increased activation of NMDAR, which in turn initialized the increased production of PKC $\epsilon$  and FAK, respectively.

#### **MEP: ANTIOXIDANT MECHANISM**

In addition to A $\beta$  burden, oxidative stress accumulates in aging and is involved in the pathogenesis of AD. Antioxidants that protect cells from stressors (e.g peroxides) may serve as important protective factors of cognition and neuronal longevity. Papadia *et al.*, (2008) investigated the antioxidants that are boosted in result of NMDAR activity. Mice injected with dizocilpine (MK-801), an uncompetitive antagonist of NMDAR, experienced widespread neuronal death due to oxidative damage (Papadia *et al.*, 2008). Additionally, upregulation of NMDAR resulted in increased protection from oxidative stressors such as peroxides (Papadia *et al.*, 2008). This establishes that NMDAR, and in turn MEP, initiate a downstream process resulting in antioxidative properties.

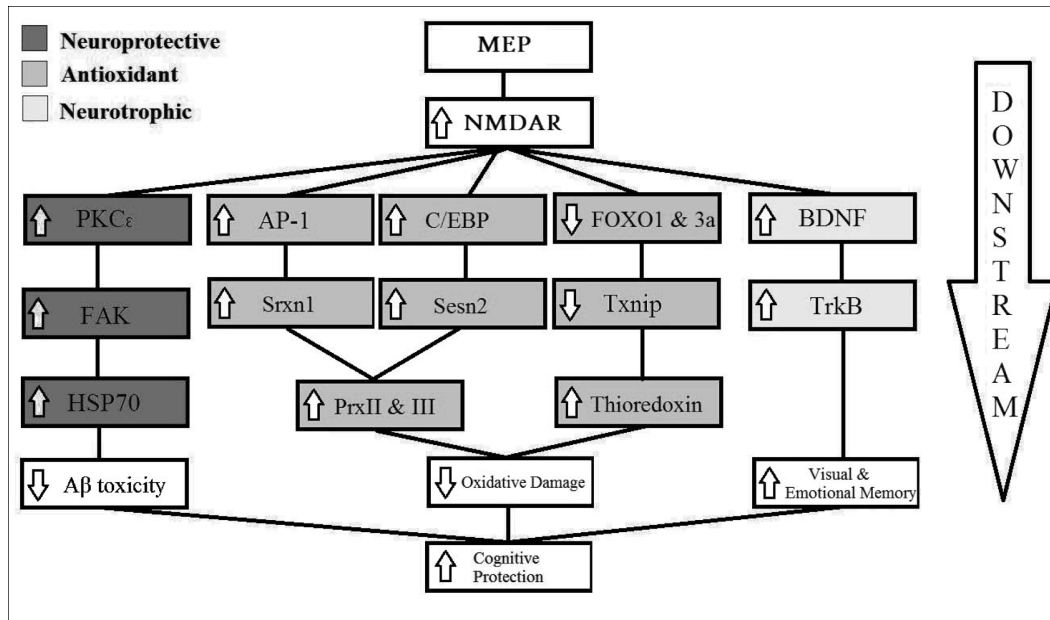
NMDAR activity protects neuronal damage from oxidative stress by directly targeting the thioredoxin-Prx system. Peroxins (Prxs) serve as cytoprotective and antioxidative proteins, in particular PrxII, PrxIII, and PrxIV (Rhee *et al.*, 2007). Prxs contain a peroxidatic cysteine residue, which in turn oxidize harmful peroxides to form cysteine sulfenic acid (-SOH). This cysteine sulfenic acid then forms a disulfide bond with the resolving cysteine, which is in turn reduced by thioredoxin (Wood *et al.*, 2003). However, during pathogenesis, oxidative stress can increase and over-oxidization of the Prxs result in sulfinic (-SO<sup>2</sup>H) or sulfonic (-SO<sup>3</sup>H) acid formation (Papadia *et al.*, 2008). This creates an over-burdened system rendering the peroxidase ineffective, allowing for oxidative damage. Typically, thioredoxin facilitates the effectiveness of the Prxs, but when sulfinic or sulfonic acid is formed by

increased levels of peroxides, thioredoxin's effectiveness is rendered useless (Papadia *et al.*, 2008). In order to protect from neuronal oxidative stress associated with AD and cognitive decline, the reduction of over-oxidized Prxs as well as the increase of thioredoxin activity must be established.

First, we investigate how NMDAR activity reduces the over-oxidization of PrxII, PrxIII and PrxIV. Over-oxidization resulting in peroxiredoxin sulfinic/sulfonic acid (Prx-SO<sub>2</sub>H) has traditionally thought to have been irreversible, however recent studies have suggested that it can be reduced back to the catalytically active thiol form by two ATP-dependent reductases, sestrin 2 (Sesn2) and sulfiredoxin (Srxn1). Papadia *et al.*, (2008) tested this hypothesis, and found positive results. After establishing bicuculline, a GABA<sub>A</sub> receptor antagonist, and 4-aminopyridine, a K<sup>+</sup> channel antagonist (BiC/4-AP) as an inducer of NMDAR activity, downstream effects could be observed. Cortical rat neurons were subjected to a brief, high (200μM) dose of hydrogen peroxide in order to induce Prx over-oxidation (Papadia *et al.*, 2008). BiC/4-AP treated neurons showed a significant increase in both Sesn2 and Srxn1. Additionally, induced Sesn2 and Srxn1 protein and mRNA expressions reduced cell death following hydrogen peroxide insult and significantly lowered Prx-SO<sub>2</sub>H (Papadia *et al.*, 2008). It should be noted that additional knock down tests showed that independent increases of Sesn2 and Srxn1 did not find any significant results, however the two together showed reliably significant effects.

Sesn2 was found to have a multiple binding sites for the transcription factor CCAAT enhancer binding protein (C/EBP) (Papadia *et al.*, 2008). After several tests using mutations of C/EBP, it was established that Sesn2 is largely mediated by C/EBP. Alternatively, Srxn1 is induced by AP-1. BiC/4-AP stimulation activates the AP-1 sites, and additional knock down studies confirmed that Srxn1 is activated via AP-1 sites (Papadia *et al.*, 2008). Therefore, Sesn2 is a C/EBP target gene, and Srxn1 is an AP-1 target gene. Furthermore, both are upregulated by NMDAR activity and MEP.

Furthermore, another important byproduct of increased NMDAR activation is the significant decrease in thioredoxin-interacting proteins (Txnip). Txnip binds with thioredoxin and inhibits its activity, thus promoting vulnerability to oxidative stress (Schulze *et al.*, 2004). Cortical rat cultures treated with BiC/4-AP showed a downregulation of Txnip by 60% (P=0.01) and displayed successful suppression of this pro-oxidative gene expression (Papadia *et al.*, 2008). Investigation of the activity-dependent regulation of Txnip revealed that Forkhead Box O (FOXO) is the responsible promoter. FOXO phosphorylation turns off Txnip transcription when it is



**Figure 1.** Proposed Integrated Model of Moderate Ethanol Preconditioning Resulting in Cognitive Protection

activated by protein kinase B (Pkb), which is activated by synaptic NMDAR activity (Papadia *et al.*, 2008). Therefore, it is not surprising that BiC/4-AP treated cultures showed less FOXO1 and FOXO3a expression, resulting in lower Txnip. In conclusion, Txnip is a FOXO target gene that is suppressed by NMDAR activity, resulting in an influx of thioredoxin activity and protection from oxidative insult.

### MEP: NEUROTROPHIC MECHANISM

MEP may result in enhanced memory functions. This phenomenon has been shown In Vivo in rats fed liquid diets containing no, moderate, or high amounts of ethanol (Kalev-Zylinska *et al.*, 2007). This unique animal model study exemplifies the paradoxical facilitatory effect of low-dose alcohol intake on memory via NMDAR. The abstinent rats (0% ethanol diet), the moderate-intake rats (2.5% ethanol diet, <17.4 mM BAC) and the high-intake rates (5% ethanol diet, 21.8-55.8 mM BAC) proportionally modeled human drinking behaviors (Kalev-Zylinska *et al.*, 2007). Subjects were exposed to the novel object recognition task (NOR) to examine visual recognition memory and the inhibitory avoidance test (IA) to examine associative emotional memory. Results showed that memory was enhanced for the 2.5% moderate-intake

rats compared to the high-intake and abstinent groups (Kalev-Zylinska *et al.*, 2007). This observation is reinforced by the knock down of the NR1 subunit of NMDAR. All positive effects were negated by NR1 knockdown except for emotional memory, and over-intoxication negated all effects in every condition (Kalev-Zylinska *et al.*, 2007). The exact mechanism behind this phenomenon is unknown, however Kalev-Zylinska *et al.*, (2007) suggest facilitation could be due to increases in brain-derived neurotrophic factor (BDNF) expression in the moderate-intake rats (Kalev-Zylinska *et al.*, 2007). Immunohistochemistry proved difficult, but increases of both BDNF and neurotrophic tyrosine kinase (TrkB) protein expressions showed slight but significant increases, especially in the NR1 subunit (Kalev-Zylinska *et al.*, 2007). Both BDNF and TrkB have neurotrophic implications that may result in memory facilitation, an observable downstream byproduct of MEP.

Combining the neuroprotective, antioxidative, and neurotrophic mechanisms downstream from MEP has never been suggested, and the resulting model is the first of its kind to integrate various methods resulting in cognitive protection. The proposed multi-pronged model of MEP results in the suppression of A $\beta$  toxicity, enhanced protection from oxidative damage, and improved memory (visual recognition and emotional). In conjuncture, these mechanisms could provide protection from cognitive decline associated with the AD pathology and actively delay the onset of the disease.

The first prong exhibits the decrease in A $\beta$  toxicity, suppressed via HSP70 by directly inhibiting neuronal apoptosis. Therefore, HSP70 levels can effectively delay negative effects of A $\beta$  plaques, which are implicated in AD. Additionally, many studies of aging and cognition regarding AD attribute A $\beta$  burden as the primary cause of the pathology and related cognitive decline (Peters *et al.*, 2008; Anstey *et al.*, 2009). Staving off accumulation and progression of AD and associated decline could enhance cognitive functioning and increase functional longevity. In the integrated model, HSP70 is increased by the mediators PKC $\epsilon$  and FAK, and upregulation in each respectively are a direct result of increased NMDAR activity.

The second mechanism addressed in the model is the reduction of oxidative damage through MEP mediated effects on the thioredoxin-Prx system. NMDAR activity facilitates antioxidant mechanisms in the thioredoxin-Prx system by boosting the effectiveness of thioredoxin while increasing unoxidized Prxs. Thioredoxin's effectiveness is directly inhibited by Txnip, resulting in cells being sensitized to H2O2 induced death (Schulze *et al.*, 2004). Additionally, Txnip was found to be a FOXO target gene. This is exacerbated in the AD pathological process, where FOXO1 & FOXO3a mRNA



levels are further elevated, activating increased levels of Txnip (Blalack *et al.*, 2004). Therefore our model displays the NMDAR related reduction of FOXO1 & 3a activity resulting in a downstream process increasing Thioredoxin's efficiency and aiding in the battle against harmful oxidation. Furthermore, our model shows MEP mediated decreases in the level of over-oxidized Prxs. Two reactivating genes have the unique capability of reversing over-oxidized Prxs, resulting in an influx of available antioxidants: Srxn1 and Sesn2. The upregulation of both proteins directly influence the level of available PrxII, PrxIII, and PrxIV. However, the integrated model is only concerned with PrxII and III. Only these two Prxs show cytoprotective effects in cortical neurons: PrxII protects neurons against A $\beta$  toxicity and oxygen-glucose deprivation, and PrxIII protects hippocampal neurons against excitotoxicity (Papadia *et al.*, 2008). These thiol-based antioxidants are increased by Srxn1 and Sesn2, which are targeted by AP-1 and C/EBP respectively. In turn, we display AP-1 and C/EBP upregulation initiated by increased activity in NMDAR, resulting in the downstream production of PrxII & III. Together, Prx II & III and thioredoxin could provide protection to neurons from oxidative damage and preserve cognition by protecting the vital function and integrity of cortical neurons.

The final branch of our cognitive protection model was observed utilizing in vivo studies, whereas the neuroprotective and antioxidant mechanisms were investigated primarily using in vitro studies. As discussed above, rats that were fed liquid diets with various ethanol-intake levels were subjected to emotional and visual memory tasks. It was observed that moderate-intake rats performed better than both high-intake and abstinent rats on visual and emotional memory tasks. The mediator, proposed in Kalev-Zylinska *et al.*, (2007), is the increase of the neurotrophin BDNF causing the activation of Trk-B. BDNF has been shown to be vital for long-term memory, the survival of existing neurons, and the growth of new neurons and synapses (Acheson *et al.*, 2004). Additionally, AD is associated with lowered levels of BDNF and several studies suggest that neurotrophic factors such as BDNF protect against A $\beta$  toxicity and hippocampal damage (Mattson *et al.*, 2008). In particular interest to this paper, Trk-B was found to be most elevated by MEP (Kalev-Zylinska *et al.*, 2007). BDNF activates Trk-B, increasing protein growth factors that may facilitate memory. This memory facilitation, along with other important neurotrophic implications brought on by increases of BDNF, constructs our final proposed branch of MEP mediated cognitive benefits.

In conclusion, there is no single downstream factor established by the MEP phenomenon that completely protects cognition, especially when pathology like AD is present. Therefore, the integrated model combines neuroprotective, antioxidative, and neurotrophic mechanisms in order to suggest a more multifaceted approach. By no means does this model propose a complete picture, but it does move us one step closer to further understanding MEP's vast array of biologic implications resulting in cognitive protection.

## Discussion

### OTHER POSSIBLE PROTECTIVE FACTORS MEDIATED BY MODERATE ETHANOL INTAKE

Moderate ethanol intake initiates many biological processes separate from NMDAR activation that may serve as cognitive protectants. The leading alternate argument to direct neuronal MEP facilitation is the proven effect of moderate ethanol consumption on the vascular system. Many AD risk factors in particular, as discussed earlier, are highly associated with vascular diseases and conditions. Ischemia, hypertension and obesity are all highly correlated with AD related dementia (Peters *et al.*, 2008). This established, moderate ethanol intake improves certain vascular processes, thus protecting individuals from cognitive decline by lowering AD and dementia incidence.

Alcohol's positive effect on the cardiovascular system is debated; however several studies suggest moderate amounts to be protective. Kondo (2004), as well as Ecker and Klatsky (2002), exemplify the widely accepted fact that moderate alcohol consumption increases high-density cholesterol, benefiting the cardiovascular system (Kondo *et al.*, 2004; Ecker *et al.*, 2002). Alcohol has also been shown to increase cerebral blood flow and decrease blood coagulation (Volkow *et al.*, 2006). Additionally, ethanol has been shown to be associated with an anti-inflammatory effect, which would help protect against cardiovascular disease, associated AD, and dementia (Wright *et al.*, 2006). In Vivo studies of canine ethanol intake also show reliably significant moderate-ethanol induced protection of the myocardium, relieving heart tissue from ischemic injury (Pagel *et al.*, 2002). These studies show that moderate alcohol intake may be associated with decreasing AD and dementia risk by promoting cerebrovascular benefits. However, in many of these studies, ethanol was not considered the sole variable in mediating risk factors

and future research should be conducted to determine ethanol's exclusive and direct role in cerebrovascular protection.

Moderate ethanol consumption is not limited to possible biological protective factors and may also serve as a cognitive protectant through more social means. Drinking socially could enhance cognitive functions by promoting healthy social facilitation. Additionally, studies have found that being more social may be protective. Bennett *et al.*, (2006) found that social network size and risk of cognitive impairment were inversely correlated, suggesting the beneficial effect of friends and family (Bennett *et al.*, 2006). Of course this possible protective factor is completely dependent on whether individuals find ethanol socially facilitating. Further research must be conducted to establish ethanol's effect on group situations and social networks.

Another theory of alcohol consumption's mediating effects include the possible facilitation of sleep. Alcohol is widely considered a sleep aid, and could possibly promote healthy sleep habits and help maintain a functional circadian rhythm, possibly lowering A $\beta$  accumulation in the brain (Ashley *et al.*, 2000). Excessive periods of wakefulness increase levels of orexin, which is necessary for A $\beta$  production. Additionally, chronic sleep deprivation is associated with early onset AD (Kang *et al.*, 2009). However, alcohol-induced effects on sleep vary greatly from individual to individual, and can induce arousal rather than sedation. Future studies must further investigate alcohol's effects on sleep cycles, circadian rhythm maintenance and A $\beta$  accumulation.

## **PRESCRIBING ETHANOL: POSSIBLE INTERVENTION**

Through our integrated model of MEP and our discussion of additional cognitive benefits derived from moderate ethanol consumption, it can be argued that low level intake of ethanol over a long period of time can result in significant cognitive protection. This establishes ethanol as a viable medicinal protectant to stave off AD, dementia, and related cognitive decline. Utilized at appropriate levels in conjunction with exercise and diet, ethanol may one day be a staple in the fight against cognitive aging and decline.

In addition to pre-symptomatic intake, ethanol may have a role in fighting the AD pathology once it is present. As the pathology sets in, the brain experiences an influx of glutamate metabolic damage. This excess glutamate over excites NMDAR, which causes excitotoxicity by allowing high levels of Ca<sup>2+</sup> to enter neurons. This may seem counterintuitive to the

protective effect of NMDAR activity proposed earlier, but too much  $\text{Ca}^{2+}$  results in the activation of damaging enzymes rather than initiating protective factors. However, ethanol is an NMDAR antagonist, and potentially could be used to suppress over-activation. Another NMDAR antagonist, memantine, is widely used and accepted as a treatment for advanced AD (Papadia *et al.*, 2008). Memantine suppresses  $\text{Ca}^{2+}$  production while sparing synaptic NMDAR activity. This sparing is essential because continued synaptic NMDAR activity allows for the antioxidative mechanism (displayed in model) to continue functioning (Papadia *et al.*, 2008). Future research should investigate ethanol's specific antagonistic capabilities. If ethanol is found to be effective as currently prescribed drugs, it could not only be utilized in the prevention of AD and dementia, but also during the treatment of the pathology as well.

## **PRESCRIBING ETHANOL: ISSUES**

Although ethanol could serve as a viable protective agent and possible intervention compound, it is not at this time seriously considered as a suggested method for protection or intervention. Ethanol related benefits do not outweigh the potential dangers, costs, and issues implicated with suggesting ethanol intake.

The first and most obvious concern is that ethanol is an intoxicant that possesses some harmful properties. Consumed at high levels, alcohol is associated with higher rates of cancer, neurological damage, and mental disorders (Bennett *et al.*, 2006). Furthermore, the brain is not the most sensitive organ to ethanol, and harmful liver damage can occur even at chronic low-level intake (Anstey *et al.*, 2009). Likewise, chronic alcohol abuse has been shown to facilitate progressive neurodegenerative diseases, creating a fine line between harmful and helpful effects in regards to ethanol intake (Piazza-Gardner *et al.*, 2013). Future studies must weigh the risks and benefits associated with moderate ethanol consumption before seriously considering ethanol as a suggested protective factor.

Ethanol's protective and destructive effects brings us to our second issue: calibrating and defining moderate ethanol consumption. The studies presented in this paper show great variability in their operational definition of "moderate ethanol consumption". Some measure by number of drinks over a certain amount of time, some measure by BAC, and some attempt to quantify using various self-reported measures. Even within these methods there is great variability in what constitutes as "one drink" or "high vs.

moderate” intake. This exemplifies a great inconsistency between studies, making it difficult to compare data and results. Additionally, individual variability must be taken into account. The amount of ethanol in “one drink” may impair one individual greatly while sparing another from any intoxicating effects whatsoever. Body weight, alcohol tolerance, drinking experience, and genetic disposition are only a few of many variables that must be controlled in order to accurately measure beneficial effects. The quality of the drink and the speed in which it is consumed need also to be considered. Additionally, individual variability in socialness, socioeconomic class, race, gender, ethnicity and culture may also serve as contributing factors. Future studies must account for and control these variables in order to accurately determine the benefit of MEP.

### Conclusion

We have thoroughly investigated the means by which ethanol consumption could enhance cognitive protection and have constructed a model in which moderate ethanol consumption could potentially stave off neurodegeneration. Due to the great degrees of variability and harmful physiological effects present throughout this review, ethanol consumption may never be a suggested practice to stave off AD and dementia. Although ethanol itself is unlikely to be utilized in practice, we have outlined its protective effects through various mechanisms that may assist in the discovery of more selective interventions in the future. The integrated model suggested within this paper serves as such an outline.

### References

- Acheson, A., Conover, J.C., Fandl, J.P., DeChiara, T.M., Russell, M. & Thadani, A. et al. (1995). A BDNF autocrine loop in adult sensory neurons prevents cell death. *Nature*, 374(6521), 450-453. <http://dx.doi.org/10.1038/374450a0>
- Angevaren, M., Aufdemkampe, G., Verhaar, H.J., Aleman, A. & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Syst Rev*, 16(2), CD005381. <http://dx.doi.org/10.1002/14651858.cd005381.pub2>
- Anstey, K.J, Mack, H.A. & Cherbuin, N. (2009). Alcohol consumption as a risk factor for dementia and cognitive decline: Meta-analysis of prospective

studies. *Am J Geriatr Psychiatry*, 17(7), 542-555. <http://dx.doi.org/10.1097/jgp.0b013e3181a2fd07>

Ashley, M.J., Rehm, J., Bondy, S., Single, E. & Rankin, J. (2000) Beyond ischemic heart disease: are there other health benefits from drinking alcohol? *Contemp Drug Problems*, 27(4), 735-777. <http://dx.doi.org/10.1177/009145090002700403>

Belmadani, A., Kumar, S., Schipma, M., Collins, M.,A. & Neafsey, E.J. (2004). Inhibition of amyloid- $\beta$ -induced neurotoxicity and apoptosis by moderate ethanol preconditioning. *NeuroReport*, 15(13), 2093-2096. <http://dx.doi.org/10.1097/00001756-200409150-00019>

Bennett, D., Schneider, J., Tang, Y., Arnold, S. & Wilson, R. (2006). The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurol*, 5(5), 406-412. [http://dx.doi.org/10.1016/s1474-4422\(06\)70417-3](http://dx.doi.org/10.1016/s1474-4422(06)70417-3)

Blalock, E.M., Geddes, J.W., Chen, K.C., Porter, N.M., Markesbery, W.R. & Landfield, P.W. (2004). Incipient Alzheimer's disease: Microarray correlation analyses reveal major transcriptional and tumor suppressor responses. *P Natl Acad Sci USA*, 101(7), 2173-2178. <http://dx.doi.org/10.1073/pnas.0308512100>

Budanov, A.V., Sablina, A.A., Feinstein, E., Koonin, E.V. & Chumakov, P. (2004). Regeneration of peroxiredoxins by p53-Regulated sestrins, homologs of bacterial AhpD. *Science*, 304(5670), 596-600. <http://dx.doi.org/10.1126/science.1095569>

Collins, M.A., Neafsey, E.J., Wang, K., Achille, N.J., Mitchell, R.M. & Sivaswamy, S. (2010). Moderate ethanol preconditioning of rat brain cultures engenders neuroprotection against dementia-inducing neuroinflammatory proteins: Possible signaling mechanisms. *Mol Neurobiol*, 41(2-3), 420-425. <http://dx.doi.org/10.1007/s12035-010-8138-0>

Ecker, R.R. & Klatsky, A.L. (2002). Doctor, should I have a drink? An algorithm for health professionals. *Ann NY Acad Sci*, 957(1), 317-320. <http://dx.doi.org/10.1111/j.1749-6632.2002.tb02932.x>

Giunta, B., Obregon, D., Velisetty, R., Sanberg, P.R., Borlongan, C.V. & Tan, J. (2012). The immunology of traumatic brain injury: A prime target for Alzheimer's disease prevention. *J Neuroinflamm*, 9(1), 185. <http://dx.doi.org/10.1186/1742-2094-9-185>

Gu, Y., Nieves, J.W., Stern, Y., Luchsinger, J.A. & Scarmeas, N. (2010). Food combination and Alzheimer disease risk. *Arch Neurol*, 67(6), 699-706. <http://dx.doi.org/10.1001/archneurol.2010.84>

Herbert, L.E., Scherr, P.A., Bienieas, J.L., Bennett, D.A., & Evans, D.A. (2003). Alzheimer disease in the US population: Prevalence estimates using the 2000 census. *Arch Neurol*, 60(8), 1119-1122. <http://dx.doi.org/10.1001/archneur.60.8.1119>

Kalev-Zylinska, M.L., & During, M.J. (2007) Paradoxical facilitatory effect of low-dose alcohol consumption on memory mediated by NMDA receptors. *J Neurosci*, 27(39), 10456-10467. <http://dx.doi.org/10.1523/jneurosci.2789-07.2007>

Kang, J.E., Lim, M.M., Batemean, R.J., Lee, J.J., Smyth, L.P., Cirrito, J.R. & Fujiki, N. (2009). Amyloid- $\beta$  dynamics and regulated by orexin and the sleep-wake cycle. *Science*, 326(5955), 1005-1007. <http://dx.doi.org/10.1126/science.1180962>

Klatsky, A.L., Armstrong, M.A. & Freidman, G.D. (1997). Red wine, white wine liquor, beer and risk for coronary artery disease hospitalization. *Am J Cardiol*, 80(4), 416-420. [http://dx.doi.org/10.1016/S0002-9149\(97\)00388-3](http://dx.doi.org/10.1016/S0002-9149(97)00388-3)

Kondo, K. (2004). Beer and health: Preventive effects of beer components on lifestyle-related diseases. *Biofactors*, 22(1-4), 303-310. <http://dx.doi.org/10.1002/biof.5520220160>

Lautenschlager, N.T., Cupples, L.A., Rao, V.S., Auerbach, S.A., Becker, R., Burke, J., ... Farrer, L.A. (1996). Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old? *Neurology*, 46(3), 641-650. <http://dx.doi.org/10.1212/WNL.46.3.641>

Mattson, M.P. (2008) Glutamate and neurotrophic factors in neuronal plasticity and disease. *Ann NY Acad Sci*, 1144, 97-112. <http://dx.doi.org/10.1196/annals.1418.005>

Pagel, P.S., Krolikowski, J.G., Kehl, F., Mraovic, B., Kersten, J.R. & Warltier, D.C. (2002). The role of mitochondrial and sarcolemmal K(ATP) channels in canine ethanol-induced preconditioning in vivo. *Anesth Analg*, 94(4), 841-848. <http://dx.doi.org/10.1097/00000539-200204000-00012>

Papadia, S., Soriano, F.X., Leveille, F., Martel, M.A., Dakin, K.A., Hansen, H.H., ... Hardingham, G.E. (2008). Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses. *Nat Neurosci*, 11(4), 476-487. <http://dx.doi.org/10.1038/nn2071>

- Peters, R., Peters, J., Warner, J., Beckett, N. & Bulpitt, C. (2008). Alcohol, dementia and cognitive decline in the elderly: A systematic review. *Age Aging*, 37(5), 505-512. <http://dx.doi.org/10.1093/ageing/afn095>
- Piazza-Gardner, A.K., Gaffud, T.J. & Barry A.E. (2013). The impact of alcohol on Alzheimer's disease: A systematic review. *Aging Ment Health*, 17(2), 133-146. <http://dx.doi.org/10.1080/13607863.2012.742488>
- Rhee, S.G., Jeong, W., Chang, T.S. & Woo, H.A. (2007). Sulfiredoxin, the cystein sufinic acid reductase specific to 2-Cys peroxiredoxin: its discovery, mechanism of action, and biological significance. *Kidney Int Suppl*, 72, S3-S8. <http://dx.doi.org/10.1038/sj.ki.5002380>
- Richard, F. & Pasquier, F. (2012). Can the treatment of vascular risk factors slow cognitive decline in Alzheimer's disease patients? *J Alzheimers Dis*, 32(3), 765-772. <http://dx.doi.org/10.3233/JAD-2012-121012>
- Schulze, P.C., Yoshioka, J., Takahashi, T., He, Z., King, G.L. & Lee, R.T. (2004). Hyperglycemia promotes oxidative stress through inhibition of thioredoxin function by thioredoxin-interacting protein. *J Biol Chem*, 279(29), 30369-30374. <http://dx.doi.org/10.1074/jbc.M400549200>
- Solomon, A., Kivipelto, M., Wolozin, B., Zhou, J. & Whitmer, R.A. (2009). Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dement Geriatr Cogn*, 28(1), 75-80. <http://dx.doi.org/10.1159/000231980>
- Volkow, N.D., Wang, G.J., Franceschi, D., Fowler, J.S., Thanos, P.P., Maynard, L., ... Kai Li, T. (2006). Low doses of alcohol substantially decrease glucose metabolism in the human brain. *Neuroimage*, 29(1), 295-301. <http://dx.doi.org/10.1016/j.neuroimage.2005.07.004>
- Wang, J., Ho, L., & Zhao, Z. (2006). Moderate consumption of Cabernet Sauvignon attenuates A $\beta$  neuropathology in a mouse model of Alzheimer's disease. *Faseb J*, 20(13), 2313-2320. <http://dx.doi.org/10.1096/fj.06-6281com>
- Whitmer, R.A., Gustafson, D.R., Barrett-Conner, E., Haan, M.N., Gunderson, E.P., & Yaffe, K. (2008). Central obesity and increased risk of dementia more than three decades later. *Neurology*, 71(14), 1057-1064. <http://dx.doi.org/10.1212/01.wnl.0000306313.89165>
- Wood, Z.A., Schröder, E., Robin Harris, J. & Poole, L.B. (2003). Structure, mechanism and regulation of peroxiredoxins. *Trends Biochem Sci*, 28(1), 32-40. [http://dx.doi.org/10.1016/S0968-0004\(02\)00003-8](http://dx.doi.org/10.1016/S0968-0004(02)00003-8)



Wright, C.B., Sacco, R.L., Rundek, T.R., Delman, J.B., Rabbani, L.E. & Elkind, M.S.V. (2006). Interleukin-6 is associated with cognitive function: the Northern Manhattan Study. *J Stroke Cerebrovasc*, 15(1), 34-38. <http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2005.08.009>